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Inorganic Particle Content of Foods and Drugs

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Inorganic particulate matter in foods and drugs is discussed from the standpoint of determination by optical microscopy, source, and regulatory significance. Some particulate matter may be generated as extraneous material and traced to specific operational practices during processing and production with excessive levels associated with deficiencies in good manufacturing practices. Other particles, such as talc and asbestos, may be incorporated as additives during their use in production. Data on particles in parenteral drugs are discussed generally. Specific data on glass particles in foods and sand and soil particles in spices are presented.

The U.S. Food and Drug Administration has dealt with contamination involving inorganic particulate matter in foods and drugs in a variety of ways as problems falling within the Agency's responsibilities in this area have been identified. Episodes have occurred where foreign inorganic particulate matter, such as metal, rust, glass, sand, paint, etc., has inadvertently found its way into food and drug products either by accident or lack of proper attention to hazards associated with certain conditions of manufacture. Each of these cases is evaluated on its own merits where the problem is endemic to an individual situation. However, where these problems have been widespread or common to certain classes of food and drug products, a more organized evaluation of specific particulate contamination in these products has been made.

As a general rule, particulate contamination, whether of an inorganic or organic nature, may be classified in regulatory language as falling within one or both of two categories: (1) particulate matter representing natural or unavoidable defects in foods and drugs for human use that present no health hazard and/or (2) particulate matter that may present a health hazard.

Obviously, statistically valid levels or guidelines for enforcement based on good manufacturing practice are required for the first catagory as determined by comprehensive surveys. Determination of levels, however expressed, for the second category represents a more difficult problem.

I shall discuss in this paper several examples of inorganic particles in foods and drugs to illustrate the various dimensions of the problem. The discussion is largely from the standpoint of incidence as determined by optical microscopic methodology (Figs. 1 and 2).

Particulate Matter in Parenteral Drugs

Inorganic particles in parenteral drugs are reported to include insoluble material such as glass, metal, iron rust, boiler scale, carbon, and asbestos introduced from a variety of sources. Particles in parenteral drugs come from two basic sources. These are the drug itself, and the container and closure. Those particles intrinsic to the drug may result from contaminated make-up water, precipitates in the solution, impurities, lack of adequate filtration, migration of the filtering medium (Fig. 3), and particle entrapment and subsequent release occurring in the plumbing that handles liquid drugs. Air-

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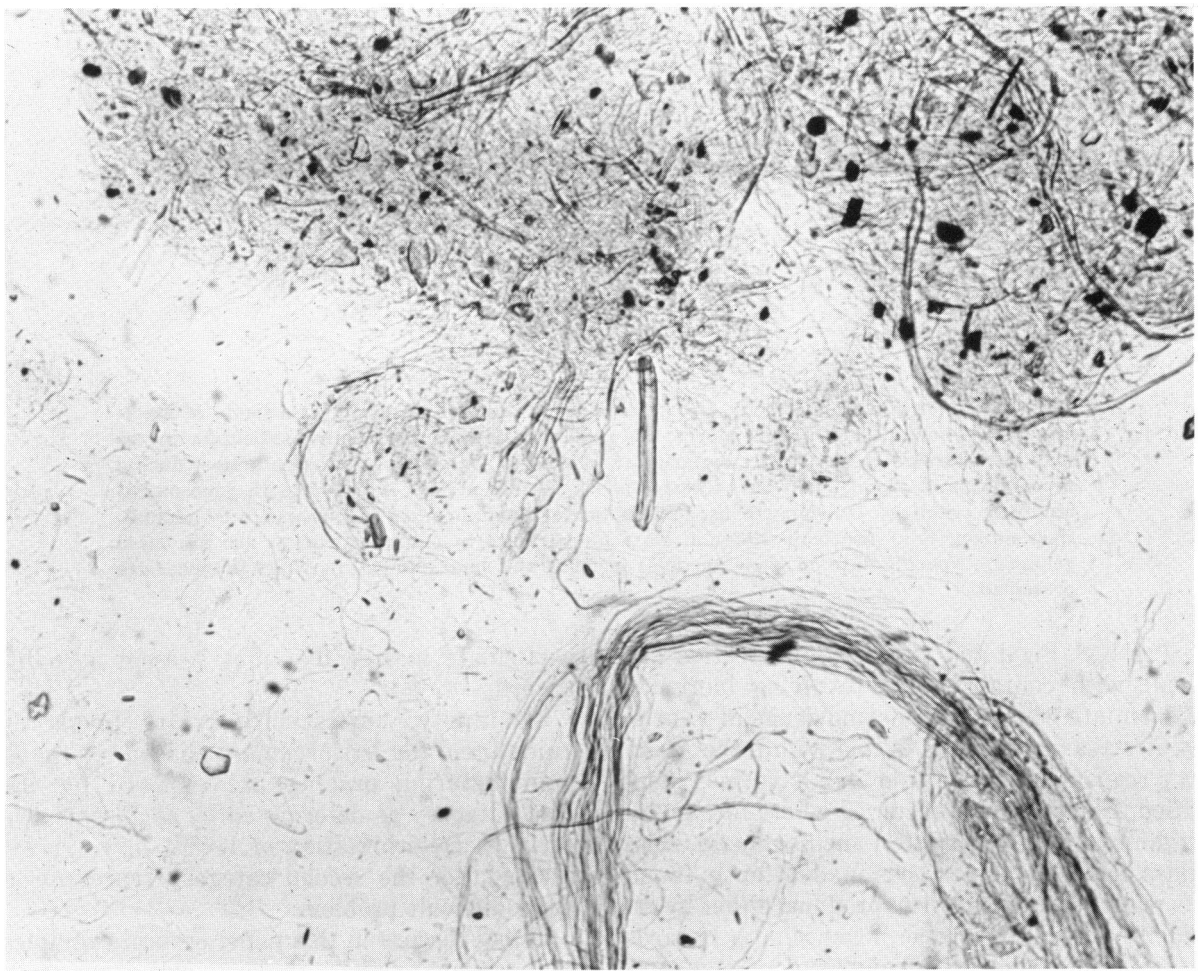

FIGURE 1. Chrysotile asbestos showing fibrillar structure and "wavy" appearance. UICC reference sample B (Canadian). ×266.

borne dust and lint may be of considerable concern. Pharmaceutical manufacturers are becoming more aware of the ubiquitous nature of particle problems. Improvements in filtration and monitoring methods are occurring frequently.

Powdered drugs designed to be reconstituted with a diluent and then injected can be a far more serious source of particles than can a solution. This is because a solution can be filtered immediately before packaging, while a powder cannot. Also, powders are more abrasive than liquids; therefore, they will generate more particles through abrasion of their surroundings. Glass particles are known to be generated in opening of sealed glass ampules containing drugs for parenteral use. Experimental data showed glass particles are incorporated into the contents when the ampules are opened with or without a scoring file. Fewer glass particles were generated when a file was used. Glass particles recovered from contents of ampules ranged in size from 30 μm to 3 mm average diameter, with most within the 50–150 μm range as determined by microscopic membrane filtration techniques.

In view of the demonstrated hazard in animals from injection of asbestos fibers FDA proposed in an announcement in the *Federal Register* of September 18, 1973 *(1)* a course of action to reduce asbestos fiber content to the minimum feasible level. The announcement proposes to accomplish this by either the

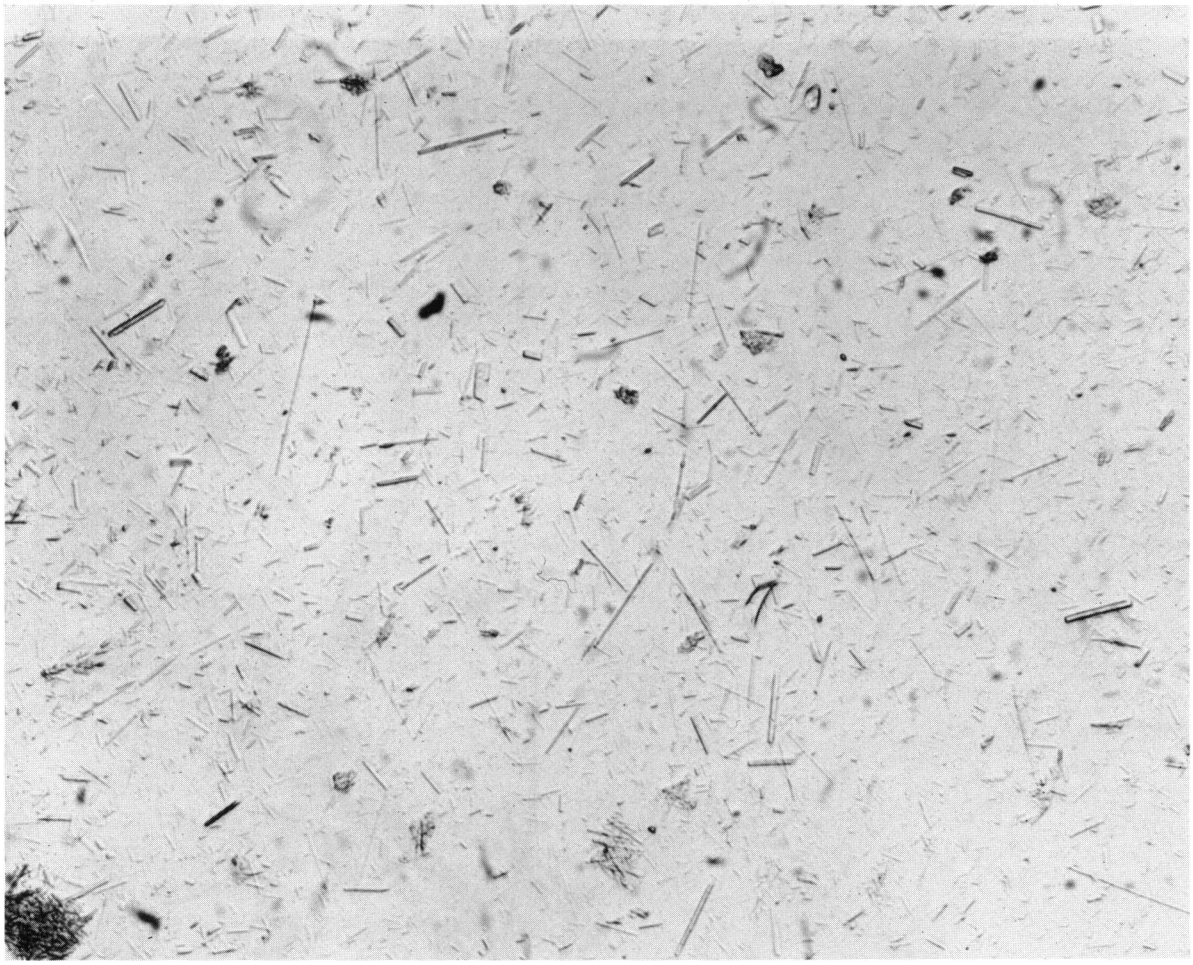

FIGURE 2. Tremolite asbestos. Straight needlelike crystals. ×266.

elimination of or change in existing filtration methods that utilize asbestos-containing filters in the production of parenteral drugs.

Workers at the FDA National Center for Antibiotic Analyses (NCAA) have emphasized one phase of the regulatory problem presented by the occurrence of various types of particulate matter in parenteral drugs and reconstituted antibiotics *(2,3)*. Because of the importance of determining the size, shape, and type of particles, these investigators selected the membrane filter microscopic method in preference to existing electronic counting devices. The absence of qualitative information from instrument reading is offset by the ease of obtaining measurements and reduction of analyst fatigue, which permit large-scale surveys of particulate matter. Thus comprehensive particulate matter surveillance should include a rapid flow technique coupled with filtering for qualitative information.

Relative to standards and specifications the authors of the NCAA papers conclude: "Even though definitive information is lacking on the relationship of particle count and size to physiological damage, it is generally accepted that specifications must be established. The most important considerations after medical significance are (1) the lowest particle count levels attainable, and (2) the capability of present methodology. In this regard, the numerical level of particles in passable samples will de-

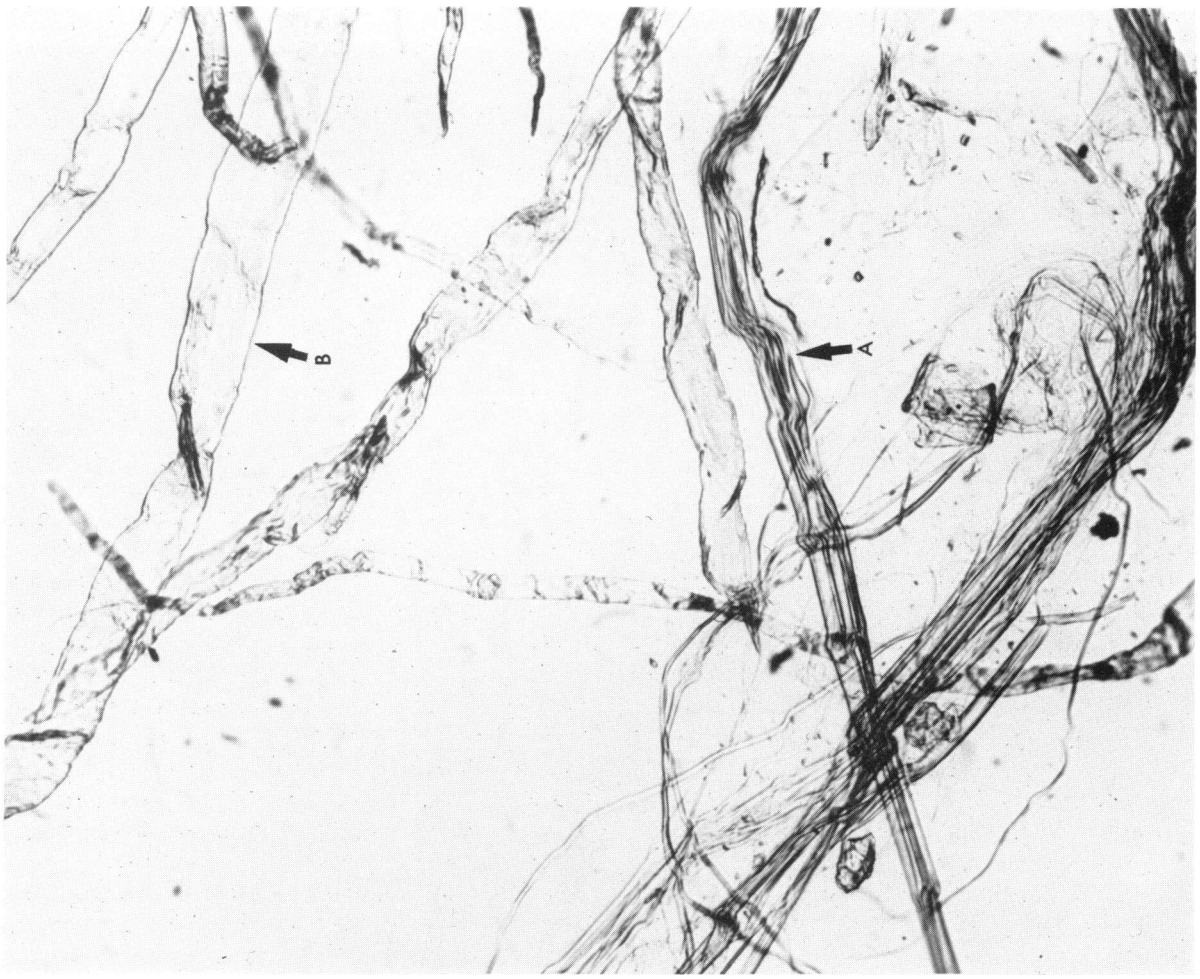

FIGURE 3. Chrysotile (A) and cotton (B) fibers from a filter pad used in plate filter for vinegar filtration. ×266.

pend upon the methodology chosen. Because of expense considerations and shortcomings of the forced-flow systems, it is quite likely that the standard method will have to be the AR-2 membrane filtration *(4)*. The one real difficulty with AR-2 is getting precise counts of particles smaller than 20 μm, but that may not be insurmountable. Lim, Turco, and Davis *(5)* were able to obtain reasonable manual counts of particles as small as 5μ."

"A necessary part of the forced-flow systems will be standard reference substances. These materials can also help in the development of filter methods. Available substances include polystyrene (Dow Chemical Co.), AC Test Dust (AC Spark Plugs), and ragweed pollen (Cutter Laboratories). There is even the possibility that the National Bureau of Standards will certify particle standards if sufficient need is demonstrated. If the standard is very nearly uniform size, it can be used as a count standard, but that is not a reality yet."

"Also a factor in establishing regulatory specifications will be the collaborative sample, since it will be necessary that different laboratories judge the same samples to be passing or failing. We have investigated the feasibility of preparing a uniformly dirty sample. Several vials of a commercially produced antibiotic, containing large numbers of particles, but not uniformly from vial to vial, were dry-mixed and stored. Later, forty portions

were weighed and analyzed by the AR-2 method. The counts of metal particles and fibers were in good agreement with those expected from the Poisson rule, but the counts of other types of particles did not agree satisfactorily with the Poisson rule. We suspect that considerable combination and breaking apart of particles took place during the mixing and analytical processes. Thus the problem of how to prepare samples for a round robin has not been solved, and will have to be further investigated so that tests and specifications can be established."

Glass Particles in Foods

Glass particles are not uncommon in a variety of foods, particularly those packaged in glass containers. Particles may be present in the containers as received from the glass manufacturer. Additional possible sources of contamination may result from rough handling of glass during transfer from cartons to filling lines, improper adjustment of filling spouts so that contact with glass would be made during filling, and breakage and chipping during capping or closure of containers.

Table 1 shows findings of glass particles in glass containers at manufacturing plants when sampled after annealing of the containers at the discharge end of the lehr (annealing oven). Results are summarized for eight plants, covering three jar sizes. The size of the container refers to finish size or size of jar opening. The small size (S) 20–28 mm, is represented by the soft drink or beer bottle; the medium (M) size, 40–48 mm, by the baby food jar; and the large size (L), 63–78 mm, by the pickle or Mason jar. A total of 2300 jars was examined. This total comprised 800 each of the small and medium sizes and 700 of the large size. The glass particles found were grouped into four size ranges: 0.1–0.4 mm; 0.5–1.0 mm; 1.1–2.0 mm; >2 mm. Of the particles found at this and other positions in the manufacturing plant, 93–96% were in the 0.1–0.4 mm size range.

Table 2 shows similar data for glass containers sampled in cartons at the warehouses of the glass manufacturers after normal handling and stacking prior to shipment to food manufacturers. The number of particles found per container increased from lehr to warehouse positions for all container sizes. The largest increase, 113%, was for the medium size (baby food) containers; the average increase, all containers, was 49.8%. Two-thirds of the particles were present at the lehr position. Generally the number of particles present at a position was greater for the larger containers.

It would appear that glass dust particles in the <0.5 mm range could be lifted and carried by an air stream of 3–5 ft/sec. Particles found in the containers were of a size which could be airborne, and the contamination found might be associated with the ventilation of the glass factories. The final section of the lehr uses a forced-air draft for cooling the containers. For the comfort of the employees much forced air ventilation (fans) is used. The containers move through the lehr and the inspection stage with open end up, so that air-borne particles could settle in the jars.

Reduction in glass particle contamination was accomplished by rearrangement of ventilation fans, better housekeeping, including immediate removal of broken ware from manufacturing

Table 1. Glass particles in glass containers at discharge annealing lehr (eight-plant composite).

Container size (opening)[a]	Number of units examined	Total number of particles	Particle size distribution, 0.1–0.4 mm	0.5–1.0mm	1.1–2.0 mm	>2.1 mm
S	800	69	63	4	1	1
M	800	67	64	2	1	0
L	700	132	122	1	5	4
Totals	2,300	268	249	7	7	5

[a] Opening size: S = 20–28 mm; M = 40–48 mm; L = 63–78 mm.

Table 2. Glass particles in glass containers in cartons in warehouse (eight-plant composite).

Container size (opening)	Number of units examined	Number of particles		Particle size distribution			
		Total	Unit	0.1–0.4 mm	0.5–1.0 mm	1.1–2.0 mm	>2.1 mm
S	800	98	0.12	97	1	0	0
M	800	141	0.18	124	10	6	1
L	700	162	0.23	155	5	1	1
Totals	2,300	401	0.17	376	16	7	2

areas, and attention to the source of air for lehr ventilation.

Table 3 summarizes findings of glass particles in glass-packaged foods. Particles were found at all plants and in all types of foods tested. Possible causes or sources of particles determined from inspectional observations are classified in Table 4, showing frequency of occurrence of various possible sources. Most frequently cited was "glass containers not cleaned before use." This was cited as a potential source of particles in 65% of the plants. The next likely cause, occurring as a potential source in 29% of the plants, was identified as "rough handling of glass before filling."

The question of possible injury to the gastrointestinal tract from ingestion of glass particles was investigated by Lehman in 1958 *(6)*, who reported that glass as well as metal fragments up to 12 mm in size fed to dogs and rabbits produced no evidence of injury as noted clinically, grossly, or histologically in the gastrointestinal tract of all animals tested.

Investigations during earlier years served to identify sources of contamination and place the problem into better perspective for institution of preventive measures. Both FDA and industry groups were in agreement as to interest in preventing or eliminating glass particles contamination regardless of the size of the particle

Table 3. Glass particles in glass-packaged foods (31 food plants), 1958.

Food	No. of jars examined	No. of jars with glass particles				Glass particles		
		Total	With 1 particle	With 2–5 particles	With >6 particles	Size, mm		Total number
						Max.	Min.	
Peanut butter 7-32 oz	356	128 (36%)	28	35	65	7.0	0.1	1,658
Pickle relish 6-32 oz.	194	16 (8%)	14	2	0	6.0	0.2	20
Spices 1-4 oz.	144	12 (8%)	8	4	0	1.3	0.1	19
Hot sauces 2-15 oz	363	32 (9%)	19	10	3	2.0	0.1	66
Mayonnaise and dressing 8-32 oz	312	14 (4.5%)	13	1	0	2.6	0.12	15
Mustard 6-24 oz	60	2 (3.3%)	2	0	0	1.0	0.2	2

Table 4. Key for possible cause or source of glass particles in glass-packaged foods (31 plants).

Key	Plants	
	No.	%
Glass containers not cleaned before use	20	65
Peanut handling procedures not adequate to remove glass pieces, if present	4	13
Rough handling of glass before filling	9	29
Glass container breakage on or near filling line	4	13
Possible contact between container and metal filling tube	4	13
Possible salvage of spilled food from floor containing broken glass	1	3
Exposed light bulb or other glass over manufacturing or packing operations	0	0
Containers shipped in "service" cases	1	3
Old vacuum filler causes breakage and contamination	1	3
Chipping of glass stoppers before and during first use	1	3
Possible splintering during mechanical application of screw caps	1	3
Metal spoon used for filling tapped against jar lip	1	3
No apparent source	6	19

or of the danger they may or may not present to the person consuming food containing such particles.

Sand and Soil Particles in Foods

Processing of food crops generally include a washing step as part of the process to remove sand and soil and other extraneous matter. However, in a number of cases the washing step is omitted for one reason or another, creating problems of excessive sand and soil or grittiness in the finished product that is objectionable to the consumer. Soil particles are common in some sun-dried foods such as spices, where gross contamination occurs from undue exposure or ineffectiveness of dry cleaning methods. Rocks are not uncommon in dried legumes and occasionally in coarse (chunky) peanut butter.

Table 5 shows the occurrence of sand and soil in various spices expressed as water-insoluble inorganic residue (WIIR). Leafy herb spices generally account for the largest levels, very likely because of the rough, irregular surfaces of such material which can entrap particles and are difficult to remove by usual dry cleaning equipment.

Table 6 shows data for WIIR in peanut butter as tabulated from an industry survey. Present limit for WIIR in peanut butter has been established at 35 mg/100 g.

Table 5. Water-insuluble inorganic residue (WIIR) in foods (spices).

Ground spice	WIIR	
	Average, mg/10	Range, mg/10g
Allspice	2.8	0 – 16.7
Chili powder	24	0 – 43.1
Paprika	28	0 – 63.4
Red pepper	30	0 –97.5
Celery seed	85.7	0 –130.5
Cinnamon	34.4	11.4– 63.4
Cloves	62.0	20.7–183.8
Coriander	111	0 –222
Cumin	56.8	51.5– 62.1
Ginger	3.6	0 – 28.8
Mace	18.5	0 – 45.4
Nutmeg	0	
Oregano	256.4	0 –645.2
Black pepper (1944)	31.9	10.8– 86.4
Black pepper (1973)	16.3	1.4–176.6
White pepper	5.3	0 – 21.2
Marjoram	302.5	23.8–479.4
Sage	138.0	46.7–393.3
Thyme	256.4	140.5–390.2

Table 6. Water-insoluble inorganic residue (sand and soil) in peanut butter.

WIIR, mg/100 g	No. of samples tested	Per cent of samples	Cumulative percentage
0	19	4.7	4.7
1–2	89	22.0	26.7
3–5	120	29.7	56.4
6–10	142	35.1	91.5
11–15	29	7.2	98.7
16–25	5	1.2	99.9
26–35	1	0.3	100.2
35	0	0	
	396	100.2	

Asbestos Fibers in Oral Drug Dosage Forms and in Foods

The literature relative to sources of asbestos fibers in foods and drugs and associated health hazards has been reviewed from the regulatory standpoint in the *Federal Register* announcement cited earlier *(1)*. A significant potential route of introduction of asbestos fibers in foods and drugs is from talc. Talc is commonly used in drugs as an excipient in compressed tablets, as a dusting powder in capsules and less frequently as a filler in the latter. It has been found in foods as a dusting powder on chewing gum and in coated rice. The common use of talc in foods is as an antisticking agent in forms used in molding food shapes. Preliminary data from the analysis of relatively few commercial samples of talc used in foods and cosmetics has shown tremolite as the only type present in those samples containing asbestos.

The method of analysis for asbestos in talc is described in the *Federal Register (1)*. The relationship of some microscopic counts to quantities in spiked samples is as follows: chrysotile in talc, 0.1% = 112/mg; 1.0% = 141/mg; tremolite in talc, 0.1%, = 125/mg.

Determination of asbestos fibers by light microscopy, even as supplemented by optical crystallography with its unique features of specificity, has certain well recognized limitations. Most important of these limitations relate to analytical situations where particle size of fibers, beyond the limits of resolution of optical microscopy, are critical to the problem. Electron microscopic techniques have filled this

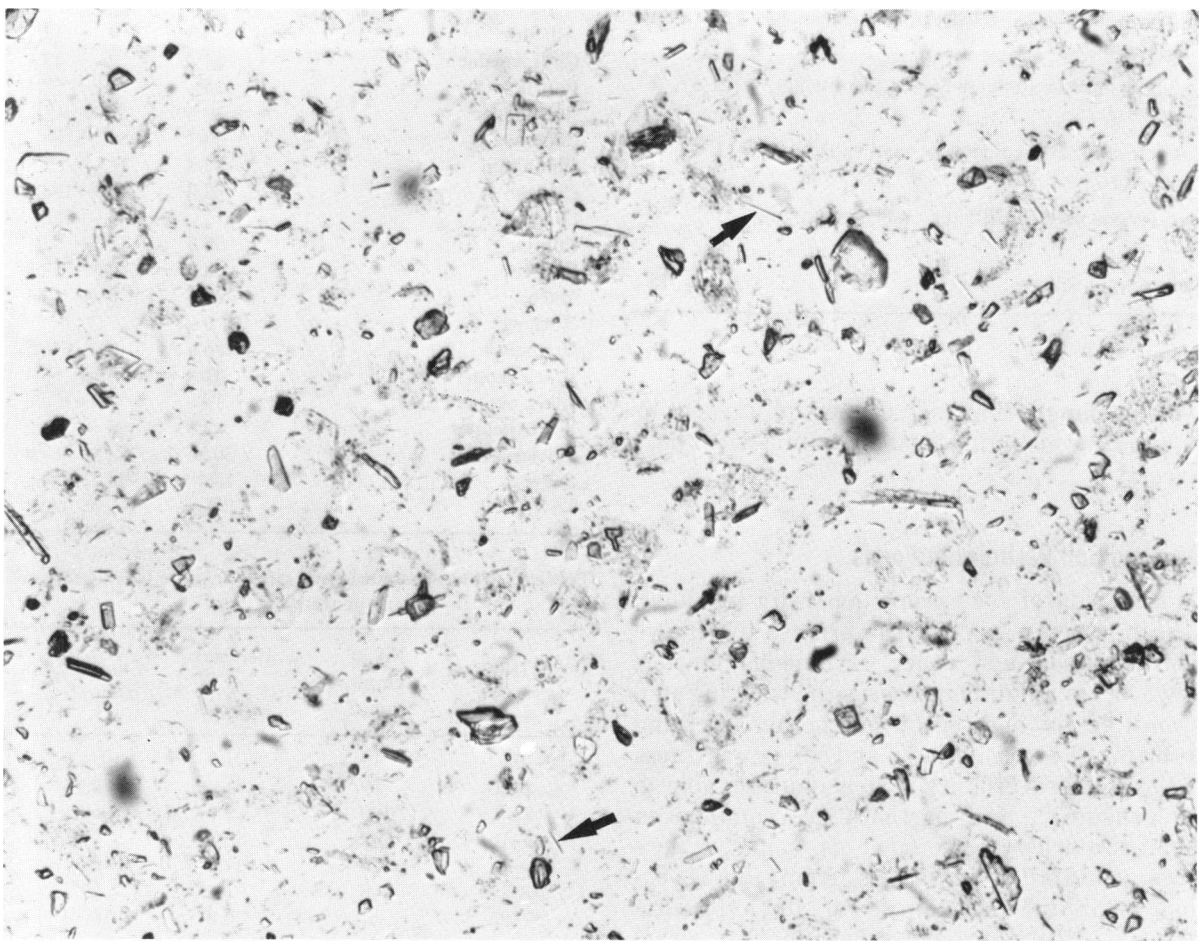

FIGURE 4. Tremolite asbestos (arrow) present in sample of talc. ×266.

need. Limitations as to quantitative precision and accuracy may be overcome in many instances by x-ray diffraction data. It is obvious from presentations at this conference that a wide spectrum of probative analytical data is desirable to meet the needs of diverse regulatory situations. A combination of analytical techniques and data and their interrelationship will provide better evaluation of these problems than single analytical characters considered in isolation from one another.

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